Animal models of drug relapse

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Outline

Extinction-based relapse models

1. Reinstatement after extinction
2. Reacquisition after extinction
3. Resurgence after extinction

Abstinence-based relapse models

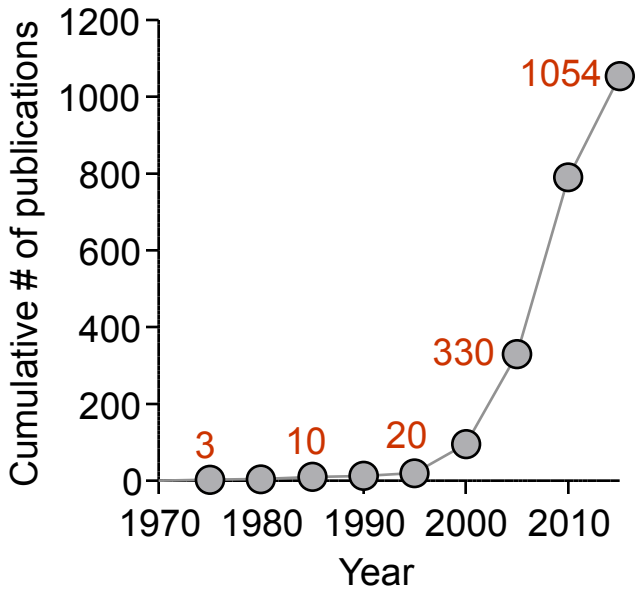
1. Forced abstinence and incubation of drug craving
2. Voluntary abstinence by introducing adverse consequences (shock punishment or electric barrier)
3. Voluntary abstinence by introducing a non-drug reward (palatable food) in a choice procedure

Three behavioral procedures:

Operant drug self-administration
Operant runway model
Pavlovian conditioned place preference (CPP)

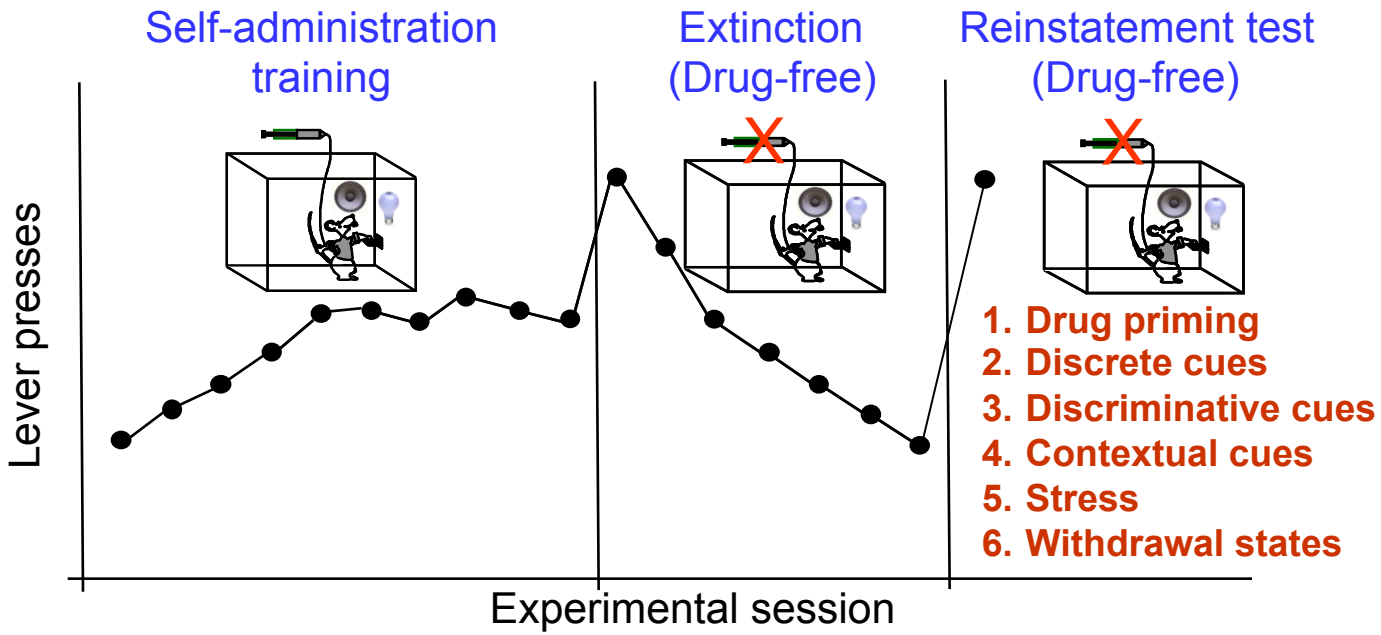
Historical perspective

Number of reinstatement/relapse studies:
1971-2012

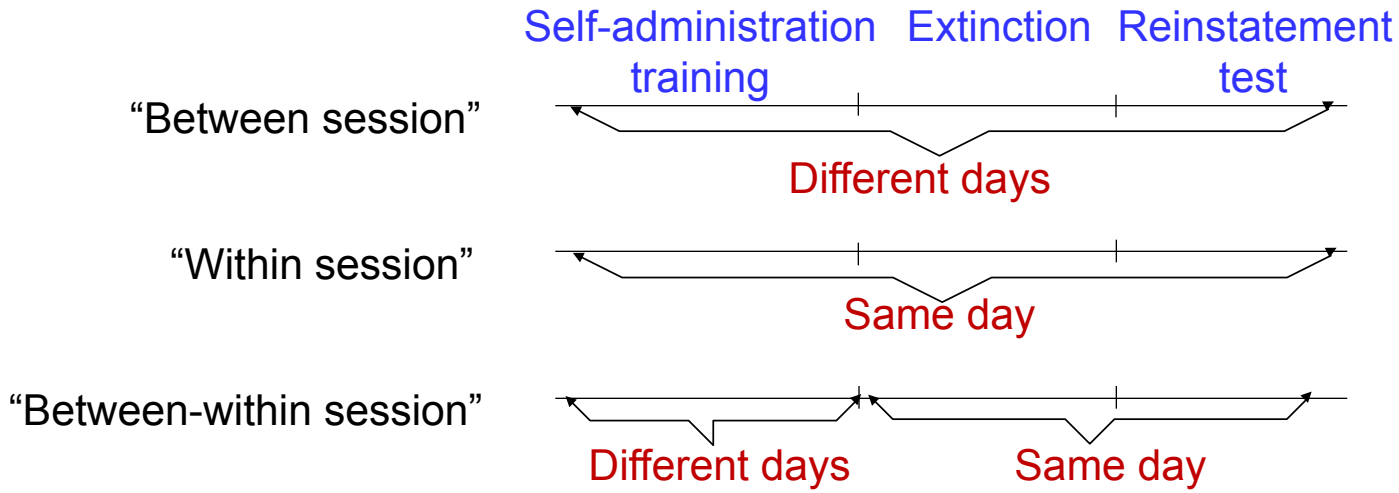


Bossert et al. Psychopharmacology 2013

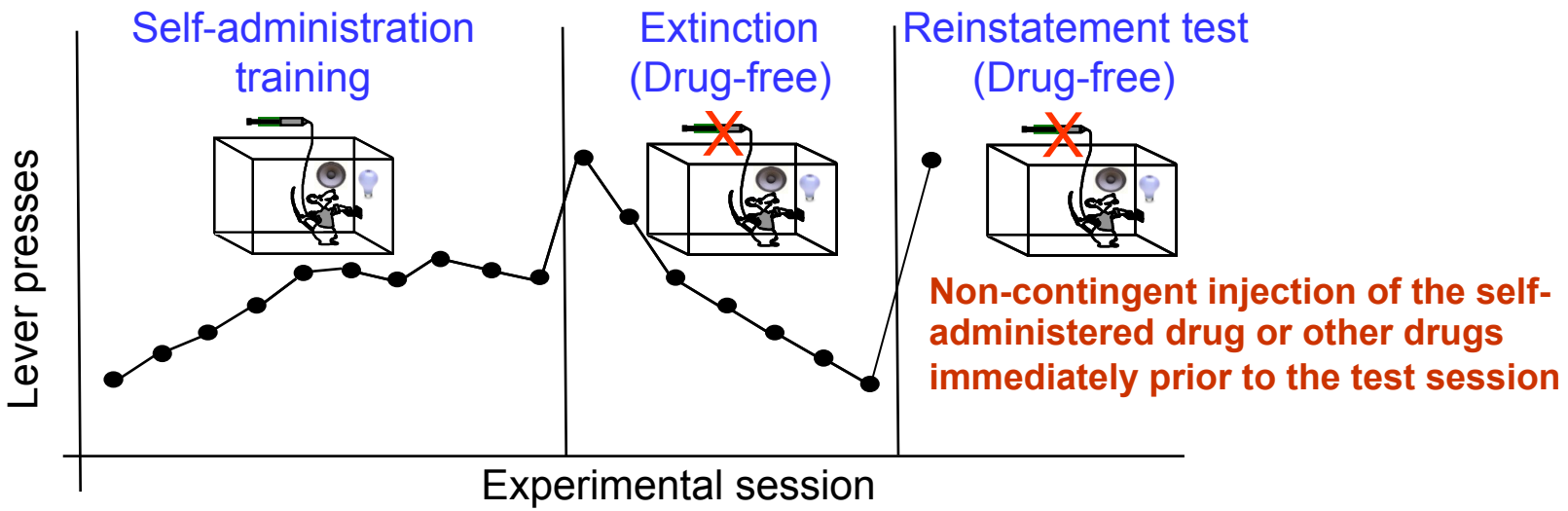
The reinstatement model



Procedural variations



1. The reinstatement model: drug priming



Key features

- A reliable manipulation with heroin, nicotine, cocaine, and methamphetamine, but not alcohol
- Psychostimulants reinstate opiate seeking but opiates do not reinstate psychostimulant seeking

Key historical citations

Stretch R, Gerber GJ, Wood SM (**1971**) Factors affecting behavior maintained by response-contingent intravenous infusions of amphetamine in squirrel monkeys. Can J Physiol Pharmacol 49: 581-589

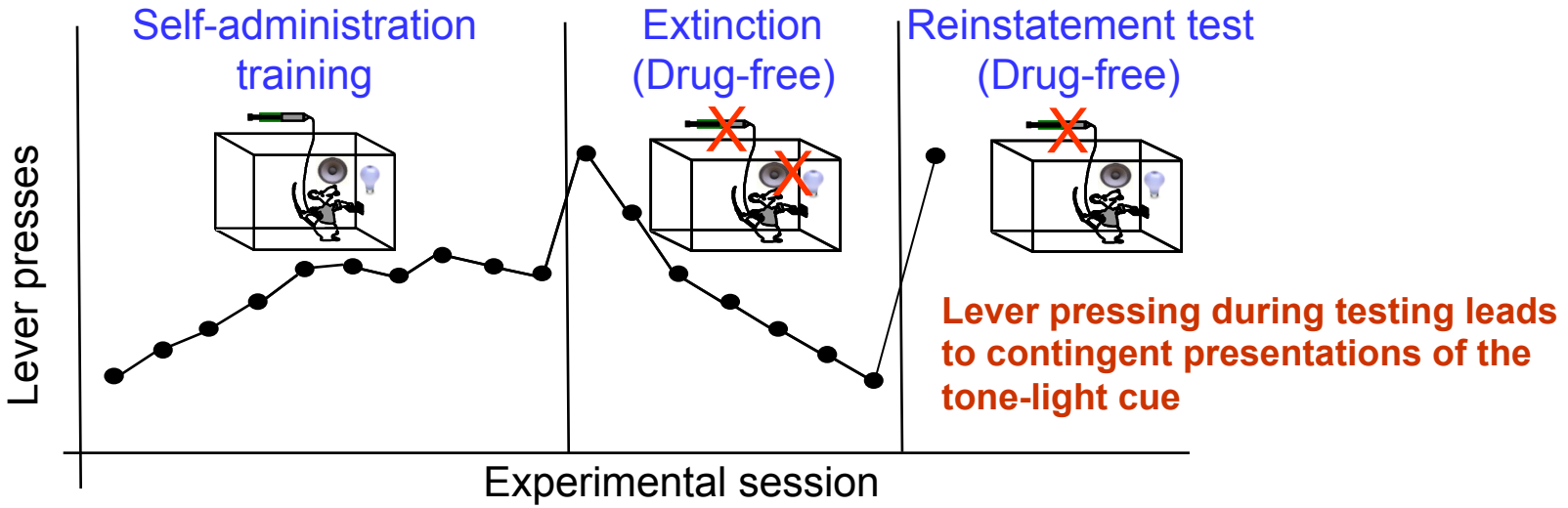
de Wit H, Stewart J (**1981**) Reinstatement of cocaine-reinforced responding in the rat. Psychopharmacology 75: 134-143

Stewart J (**1984**) Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area. Pharmacol Biochem Behav 20: 917-923

Self DW, Barnhart WJ, Lehman DA, Nestler EJ (**1996**) Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. Science 271: 1586-1589

McFarland K, Kalivas PW (**2001**) The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. J Neurosci 21: 8655-8663

2. The reinstatement model: discrete cues



Key features

- A reliable manipulation with heroin, nicotine, cocaine, methamphetamine, alcohol, and food
- The discrete compound cue functions as a conditioner reinforcer during testing
- Non-contingent discrete cue presentations are typically ineffective

Key historical citations

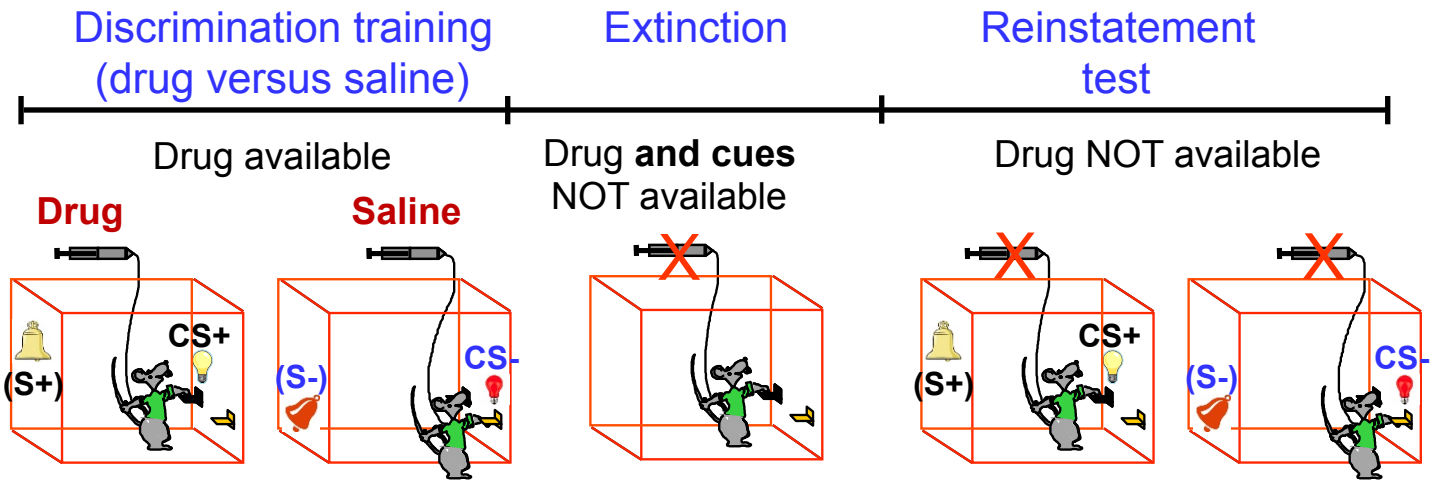
Davis WM, Smith SG (**1976**) Role of conditioned reinforcers in the initiation, maintenance and extinction of drug-seeking behavior. Pavlovian J Biol Sci 11: 222-236

Meil WM, See RE (**1996**) Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse, Behav. Pharmacol. 7, 754-763.

Meil WM, See RE (**1997**) Lesions of the basolateral amygdala abolish the ability of drug associated cues to reinstate responding during withdrawal from self-administered cocaine. Behav Brain Res 87: 139-148

McLaughlin J, See RE (**2003**) Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. Psychopharmacology 168:57-65

3. The reinstatement model: discriminative cues



Key features

- A reliable manipulation with heroin, nicotine, cocaine, methamphetamine, alcohol, and food
- Highly resistant to extinction likely due to the fact that neither the S+ nor the CS+ are presented during extinction

Key historical citations

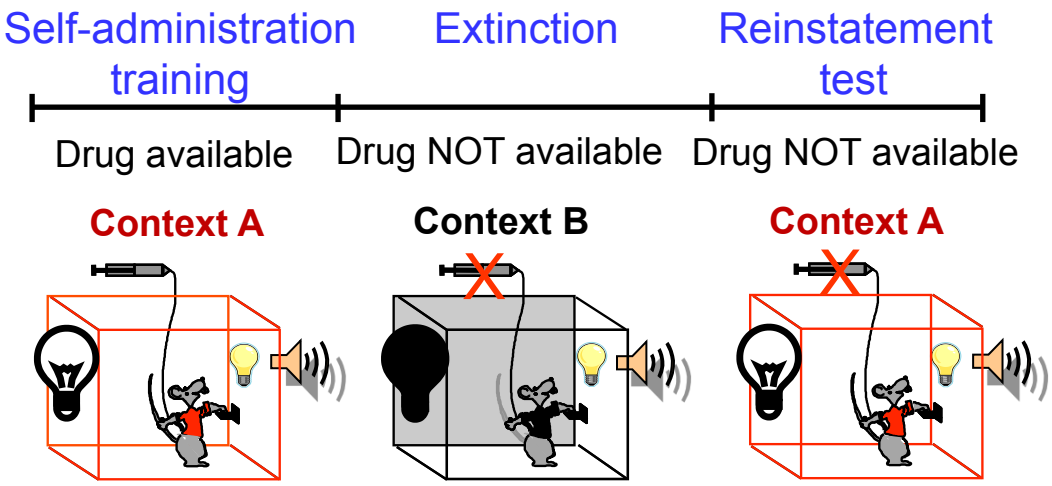
Weiss F, Maldonado-Vlaar CS, Parsons LH, Kerr TM, Smit DL, Ben-Shahar O (**2000**) Control of cocaine-seeking behavior by drug-associated stimuli in rats: effects on recovery of extinguished operant-responding and extracellular dopamine levels in amygdala and nucleus accumbens. Proc Natl Acad Sci (USA) 97:4321-4326.

Ciccocioppo R, Sanna PP, Weiss F (**2001**) Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: reversal by D(1) antagonists. Proc Natl Acad Sci (USA) 98:1976-81.

Weiss F, Martin-Fardon R, Ciccocioppo R, Kerr TM, Smith DL, Ben-Shahar O **(2001**) Enduring resistance to extinction of cocaine-seeking behavior induced by drug-related cues. Neuropsychopharmacology 25:361-372.

4. The reinstatement model: contextual cues

(Based on an ABA renewal procedure; Bouton and Bolles, 1979)



Differences between Contexts A and B:

--Tactile cues
--Auditory cues
--Visual cues
--Circadian cues
-Olfactory cues

Key features

- A reliable manipulation with heroin, nicotine, cocaine, methamphetamine, alcohol, and food
- Context-induced reinstatement is more robust in the presence of the extinguished discrete cues

Key historical citations

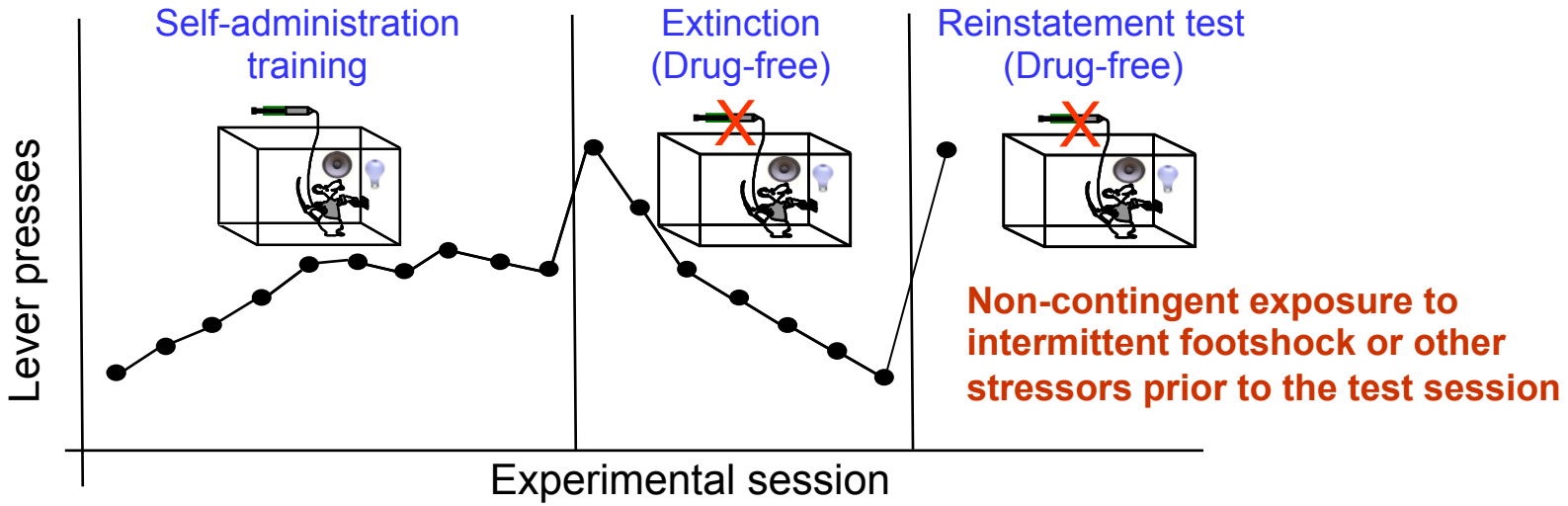
Crombag HS, Shaham Y (**2002**) Renewal of drug seeking by contextual cues after prolonged extinction in rats. Behav Neurosci 116:169-173.

Fuchs RA, Evans KA, Ledford CC, Parker MP, Case JM, Mehta RH, See RE **(2005**) The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. Neuropsychopharmacology 30:296-309.

Hamlin AS, Blatchford KE, McNally GP (**2006**) Renewal of an extinguished instrumental response: neural correlates and the role of D1 dopamine receptors. Neuroscience 143:25-38.

Bossert JM, Poles GC, Wihbey KA, Koya E, Shaham Y **(2007**) Differential effects of blockade of dopamine D1-family receptors in nucleus accumbens core or shell on reinstatement of heroin seeking induced by contextual and discrete cues. J Neurosci 27:12655-12663.

5. The reinstatement model: stress



Key features

- Footshock-induced reinstatement is context-specific
- The reinstatement effect is stressor-specific and more reliable after extended access drug self-administration
- Stress-induced reinstatement is dependent on the presence of the extinguished discrete cues during testing

Key historical citations

Carroll ME (**1985**) The role of food deprivation in the maintenance and reinstatement of cocaine-seeking behavior in rats. Drug Alcohol Dependence 16:95-109..

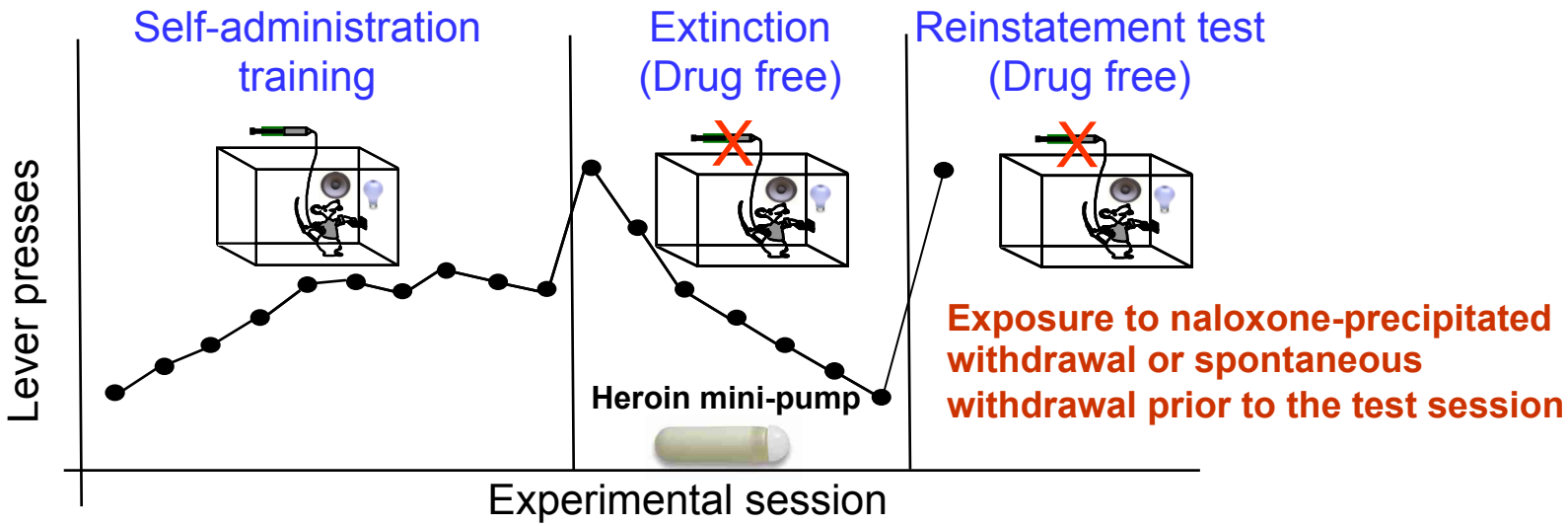
Shaham Y, Stewart J (**1995**) Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. Psychopharmacology (Berl) 119:334-341.

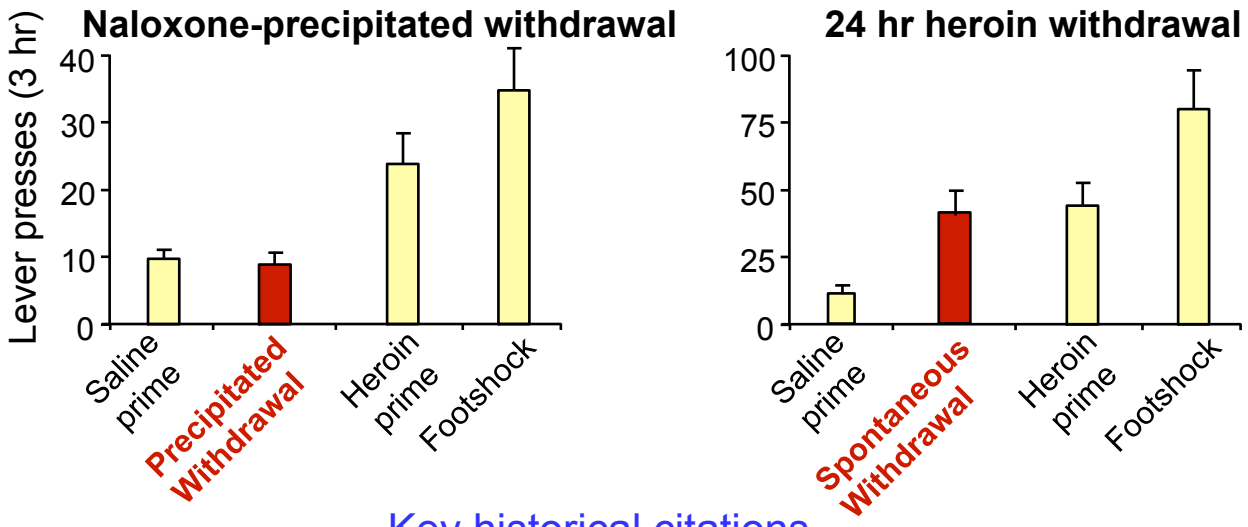
Shaham Y, Funk D, Erb S, Brown TJ, Walker CD, Stewart J (**1997**) Corticotropin-releasing factor, but not corticosterone, is involved in stress-induced relapse to heroin-seeking in rats. J Neurosci 17:2605-2614.

Shaham Y, Highfield D, Delfs JM, Leung S, Stewart J (**2000**) Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of the locus coeruleus noradrenergic neurons. Eur J Neurosci 12:292-302.

McFarland K, Davidge SB, Lapish CC, Kalivas PW (**2004**) Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. J Neurosci 24:1551-1560.

6. The reinstatement model: withdrawal states



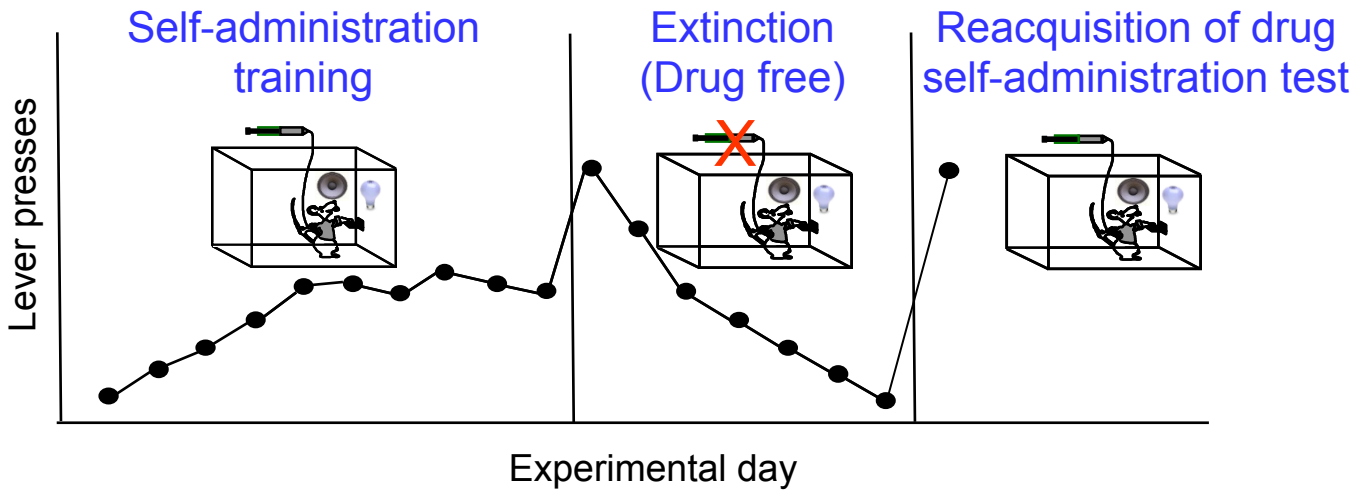


Key historical citations

Stewart J, Wise RA (**1992**) Reinstatement of heroin self-administration habits: morphine prompts and naltrexone discourages renewed responding after extinction. Psychopharmacology 108:79-84.

Shaham Y, Rajabi H, Stewart J (**1996**) Relapse to heroin-seeking in rats under opioid maintenance: the effects of stress, heroin priming, and withdrawal. J Neurosci 16:1957-1963.

The reacquisition model



Key features

- More closely mimics the human condition
- Interpretation of intake data in reference to increase or decrease in drug-taking behavior is not straightforward
- Neurobiological mechanisms appear distinct from those underlying drug seeking in reinstatement/relapse studies

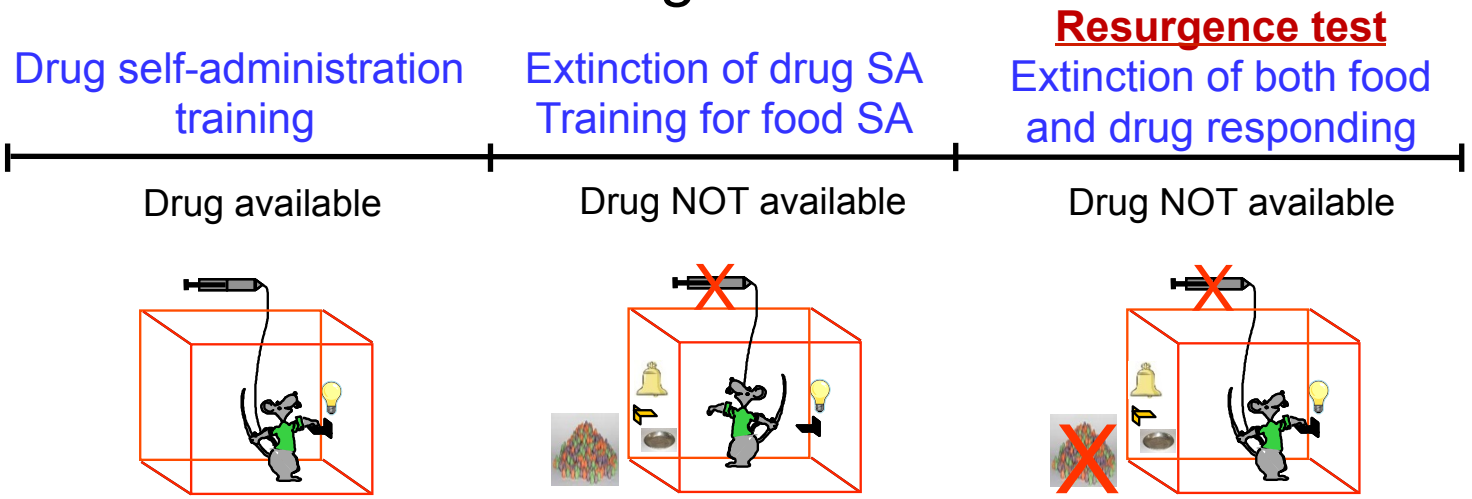
Key historical citations

Carnicella S, Kharazia V, Jeanblanc J, Janak PH, Ron D (**2008**) GDNF is a fast-acting potent inhibitor of alcohol consumption and relapse. Proc Natl Acad Sci U S A 105:8114-8119.

Willcocks AL, McNally GP (**2013**) The role of medial prefrontal cortex in extinction and reinstatement of alcohol-seeking in rats. Eur J Neurosci 37:259-268.

Millan EZ, Milligan-Saville J, McNally GP (**2013**) Memory retrieval, extinction, and reinstatement of alcohol seeking. Neurobiol Learn Mem 101:26-32

The resurgence model



Key features

- Thought to mimic the human condition of loss of non-drug reward leads to relapse
- Difficult to study mechanisms, because testing includes lever-presses under extinction for both drug and food

Key historical citations

Podlesnik CA, Jimenez-Gomez C, Shahan TA (**2006**) Resurgence of alcohol seeking produced by discontinuing non-drug reinforcement as an animal model of drug relapse. Behavioural Pharmacology 17:369-374

Quick SL, Pyszczynski AD, Colston KA, Shahan TA (**2011**) Loss of Alternative Non-Drug Reinforcement Induces Relapse of Cocaine-Seeking in Rats: Role of Dopamine D1 Receptors. Neuropsychopharmacology 36:1015-1020.

Limitations of the extinction-based reinstatement models

- Suppression of drug seeking by operant extinction training does not model human abstinence
- In humans, abstinence is typically due to three main reasons:
  1. Forced abstinence (e.g., inpatient treatment, incarceration)
  2. Self-imposed abstinence due to adverse consequences of using drugs
  3. Self-imposed abstinence due to availability of alternative non-drug rewards

Abstinence-based relapse models

1. Forced abstinence and incubation of drug craving
2. Voluntary abstinence by introducing adverse consequences (punishment or electric barrier)
3. Voluntary abstinence by introducing a non-drug reward (palatable food) in a choice procedure

Forced abstinence and incubation of drug craving

Drug self-administration (10-14 days)

Withdrawal (abstinence) period:

Extinction tests for drug seeking in a drug-free state

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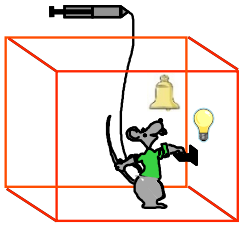
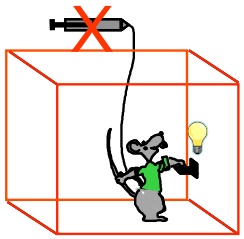
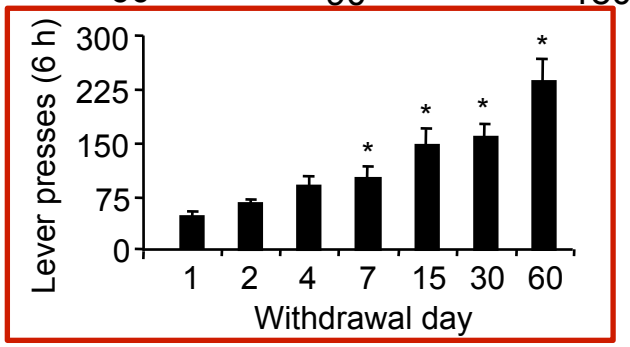






Key features

- Incubation of craving is observed with heroin, cocaine, methamphetamine, nicotine, alcohol, and sucrose
- Incubation is more robust after extended access self-administration training
- Incubation of drug craving is more robust in adult versus adolescent rats and is inhibited by enrichment

Key historical citations

Youtz REP (**1938**) The change with time of a Thorndikian response in the rat. J Exp Psychol 23:128-140.

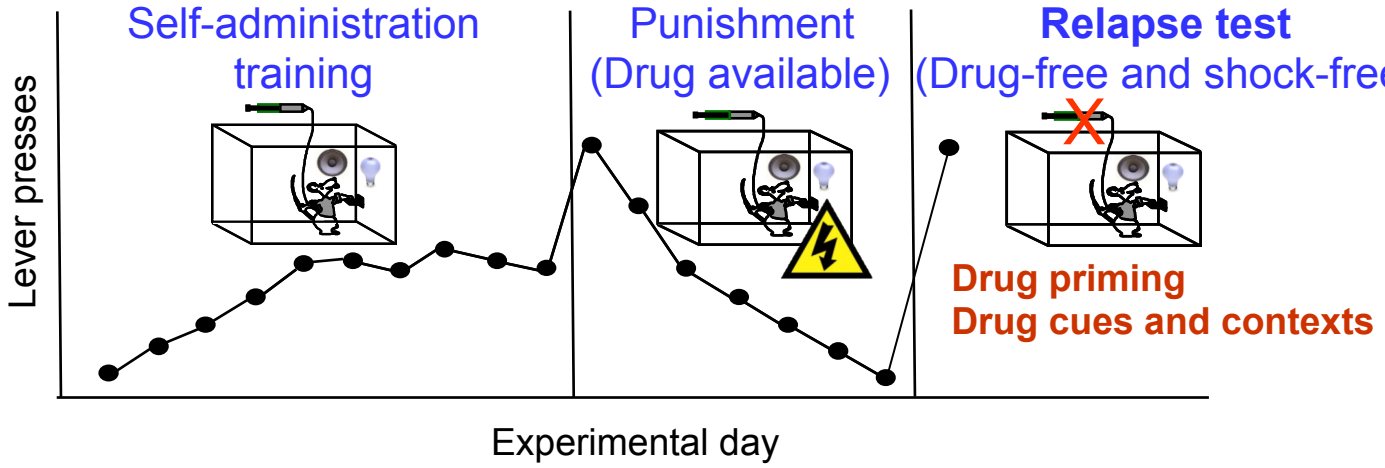
Tran-Nguyen TL, Fuchs RA, Coffey GP, O'Dell LE, Baker DA, Neisewander JL (**1998**) Time-dependent changes in cocaine-seeking behavior and dopamine overflow in the amygdala during cocaine withdrawal. Neuropsychopharmacology 19:48-59.

Shalev U, Morales M, Hope B, Yap J, Shaham Y (**2001**) Time-dependent changes in extinction behavior and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. Psychopharmacology 156:98-107.

Grimm JW, Hope BT, Wise RA, Shaham Y (**2001**) **Incubation of cocaine craving after withdrawal**. Nature 412:141-142.

Fuchs RA, Branham RK, See RE (**2006**) Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. J Neurosci 26:3584-3588.

Punishment-imposed voluntary abstinence relapse model



Key features

- Punishment is a highly effective method to inhibit drug self-administration
- Punishment procedures were used to demonstrate relapse after drug priming, drug cues and context exposure

Key historical citations

Smith SG, Davis WM (**1974**) Punishment of amphetamine and morphine self-administration behavior. Psychol Rec 24:477-480.

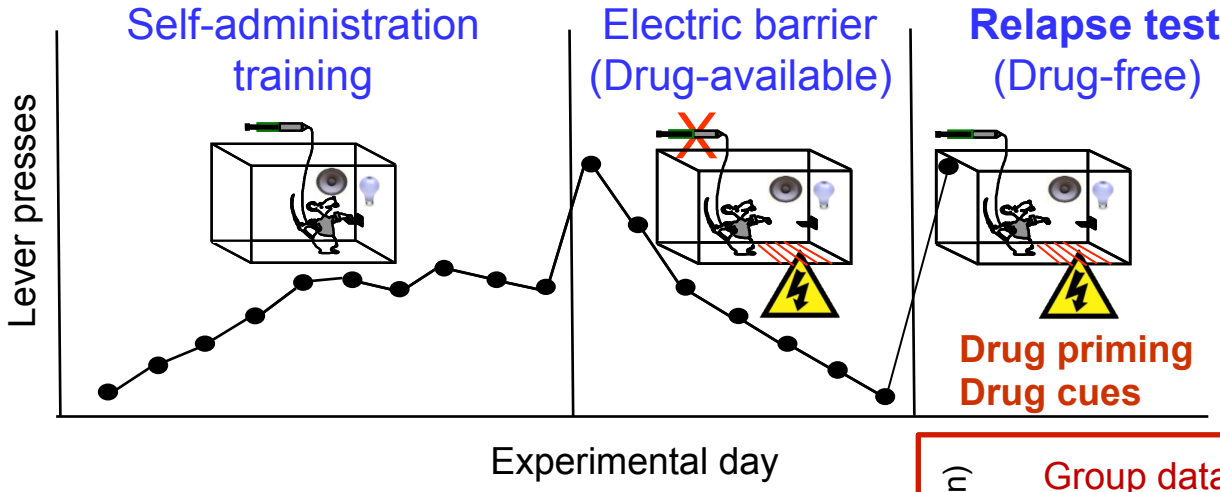
Panlilio L, Thorndike E, Schindler C **(2003**) Reinstatement of punishment-suppressed opioid self-administration in rats: an alternative model of relapse to drug abuse. Psychopharmacology 168:229-235.

Panlilio LV, Thorndike EB, Schindler CW (**2005**) Lorazepam reinstates punishment-suppressed remifentanil self-administration in rats. Psychopharmacology 179:374-382.

Marchant NJ, Khuc TN, Pickens CL, Bonci A, Shaham Y (**2013**) Context-induced relapse to alcohol seeking after punishment in a rat model. Biological psychiatry 73:256-262.

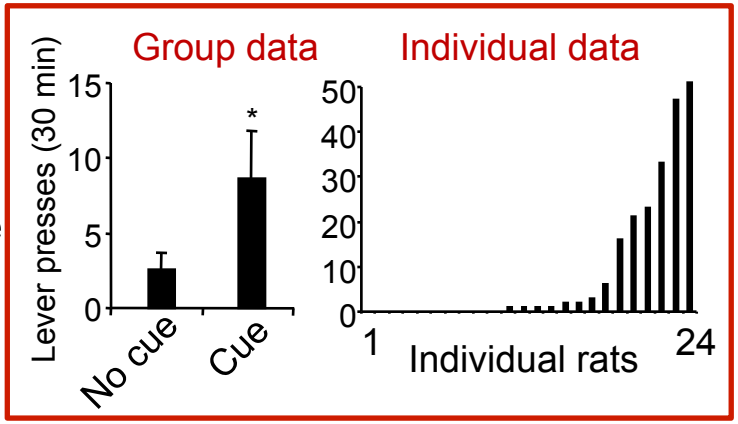
Krasnova IN, Marchant, NJ, Ladenheim B McCoy MT, Panlilio LV, Bossert JM, Shaham Y, Cadet JL (**2014**) Incubation of methamphetamine craving after punishment-induced abstinence. Neuropsychopharmacology 39: 2008–2016

Electric barrier-imposed voluntary abstinence relapse model



Key features

- Large individual differences in the relapse tests
- The procedure can be used to study individual variability in relapse



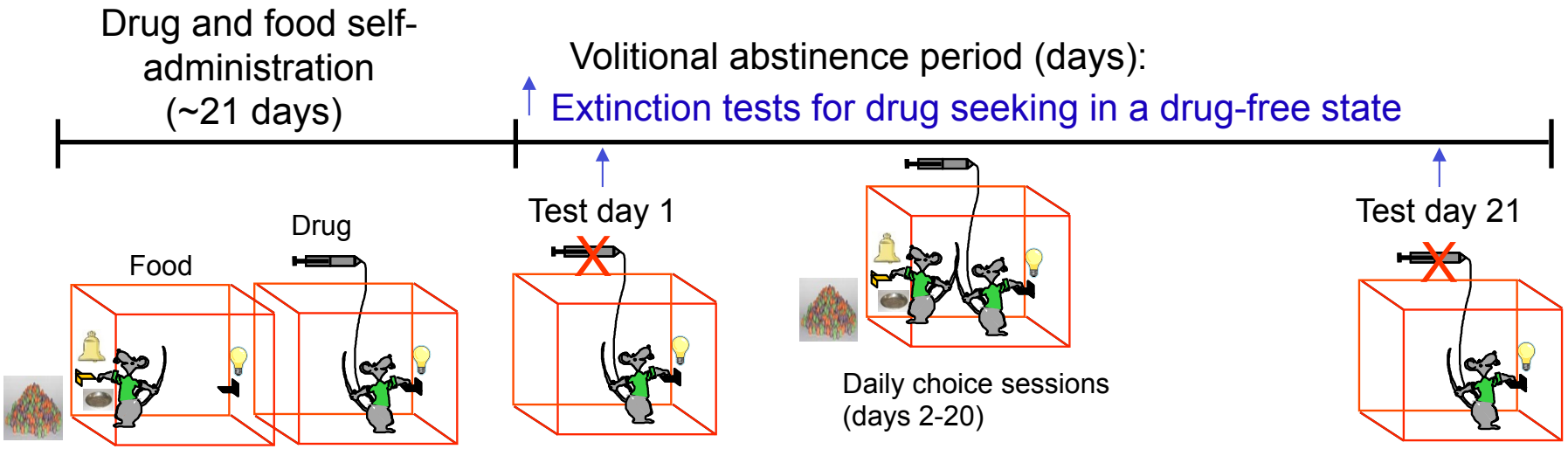
Key historical citations

Cooper A, Barnea-Ygael N, Levy D, Shaham Y, Zangen A (**2007**) A conflict rat model of cue-induced relapse to cocaine seeking. Psychopharmacology 194:117-125.

Peck JA, Wercberger R, Kariyeva E, Ranaldi R (**2013**) Cue-induced resumption of heroin and cocaine seeking in rats using a conflict model of abstinence and relapse. Psychopharmacology 228:651-658.

Saunders BT, Yager LM, Robinson TE (**2013**) Cue-evoked cocaine "craving": role of dopamine in the accumbens core. J Neurosci 33:13989-14000.

Alternative reward choice-based voluntary abstinence relapse model



Key features

- The availability of an alternative non-drug palatable food reward can completely inhibit cocaine or methamphetamine self-administration in over 90% of the rats, even under extended access conditions

Key historical citations

Lenoir M, Serre F, Cantin L, Ahmed SH (**2007**) Intense sweetness surpasses cocaine reward. PloS One 2:e698

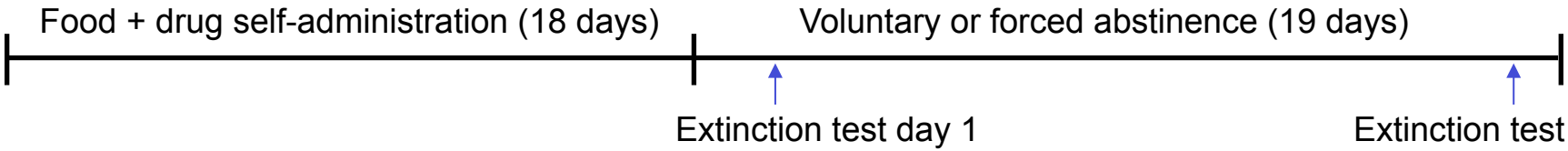
Cantin L, Lenoir M, Augier E, Vanhille N, Dubreucq S, Serre F, Vouillac C, Ahmed SH (**2010**) Cocaine is low on the value ladder of rats: possible evidence for resilience to addiction. PloS One 5:e11592

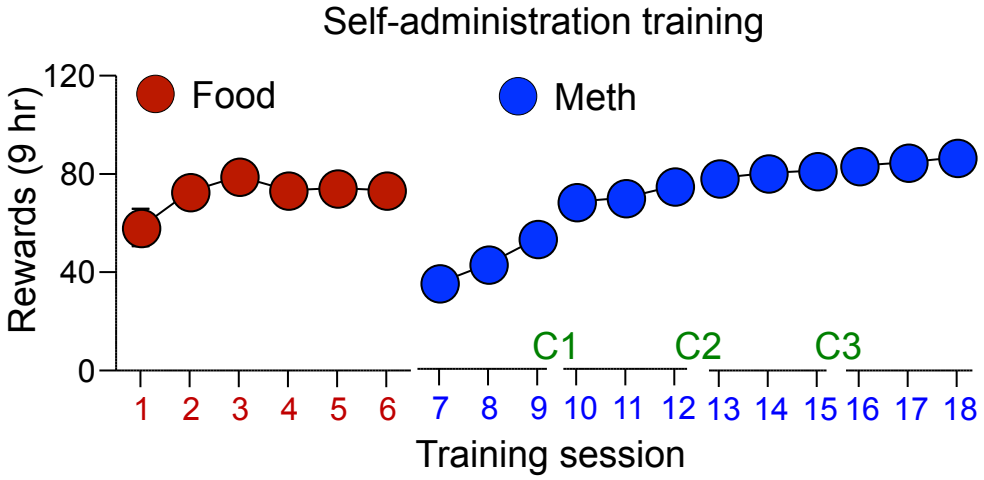
Caprioli D, Zeric T, Thorndike E, Venniro M (2014) Persistent and inflexible palatable food preference in rats with a history of limited and extended access methamphetamine self-administration. Addiction Biology (in press)

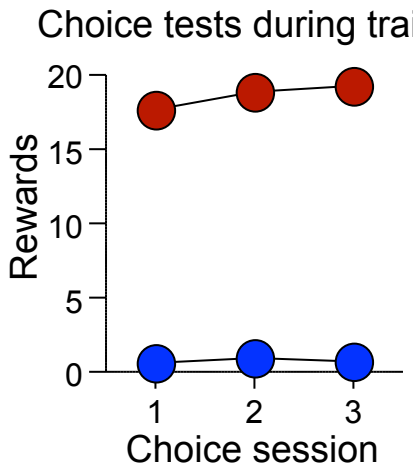
Caprioli, Venniro et al. Effect of the novel positive allosteric modulator of $mGluR_2$ AZD8529 on incubation of methamphetamine craving after prolonged voluntary abstinence (2015) Biological Psychiatry (accepted pending revisions)

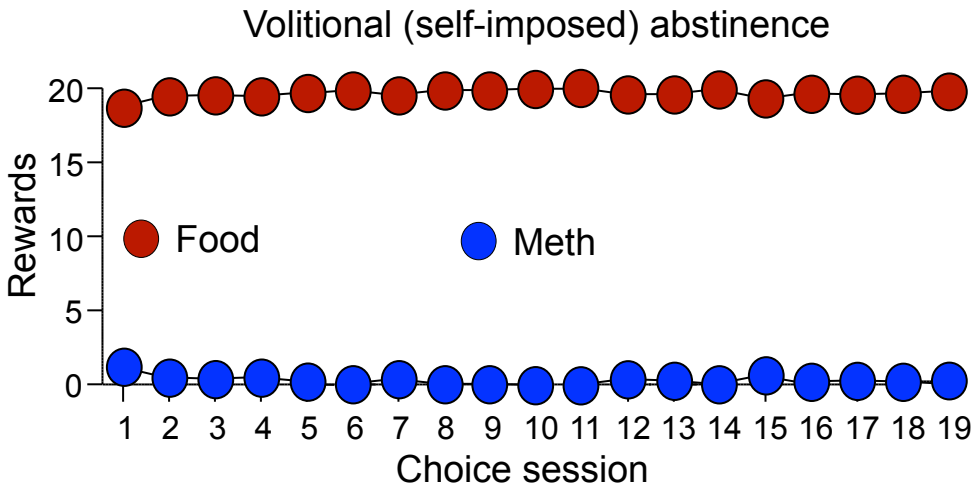
Incubation of methamphetamine craving after voluntary abstinence

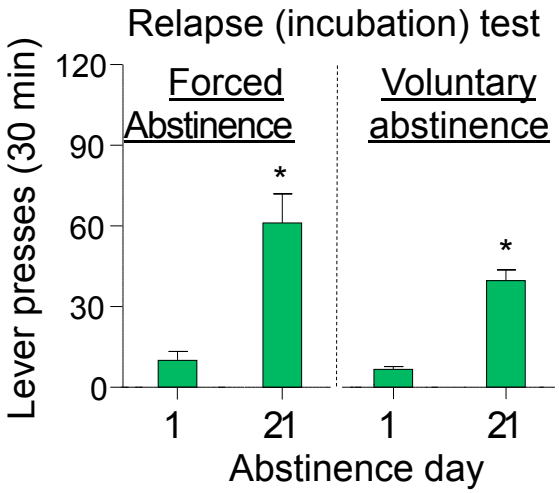
(Training: 9 h/day for 12 days)







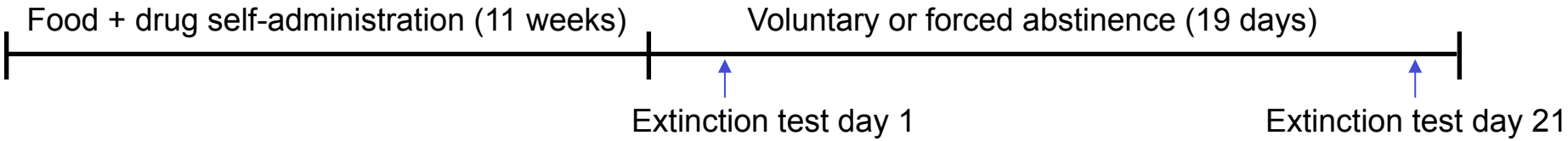


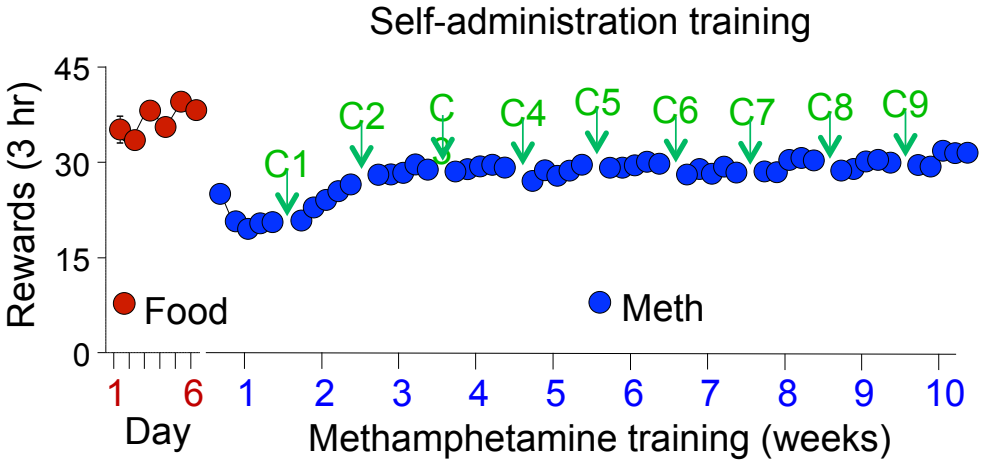


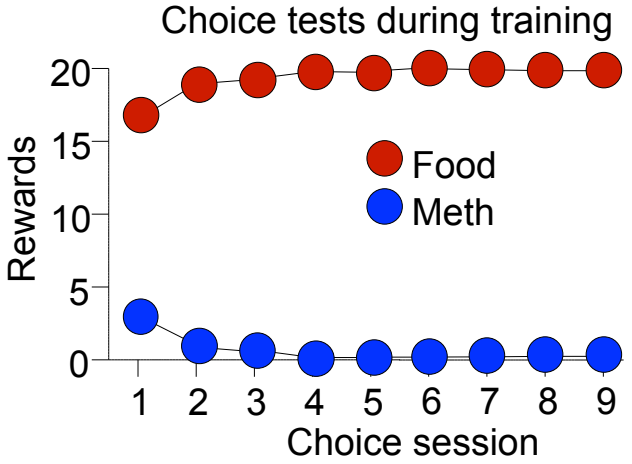
Caprioli et al (2015) Biol Psychiatry

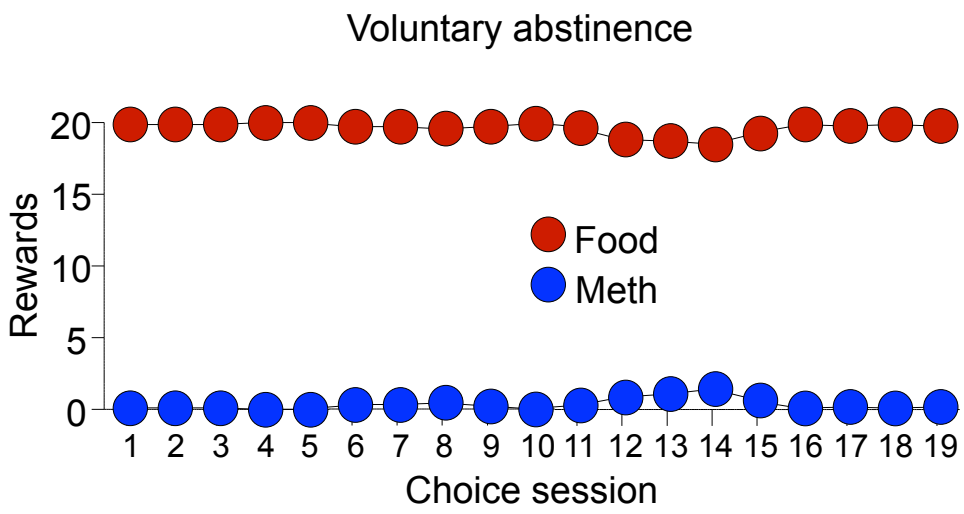
Incubation of methamphetamine craving after voluntary abstinence

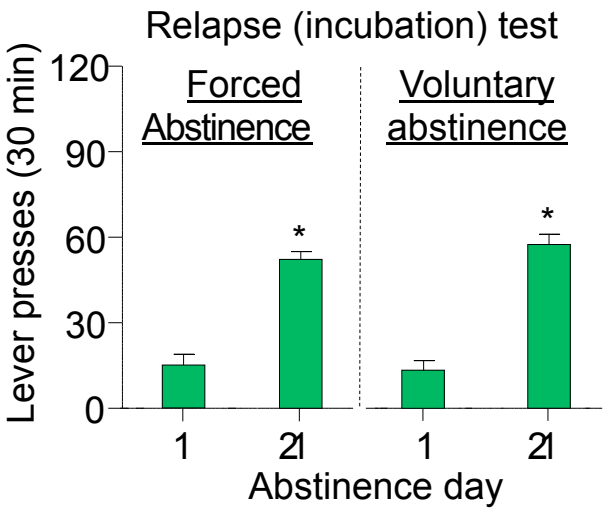
(Training: 3 h/day for 50 days)











On the validity of animal models

"All models are wrong; some models are useful"
George Box, 1979

"The best material model for a cat is another, or preferably the same cat"
Norbert Wiener, 1945

Shaham Y, Erb S, Stewart J (2000) Stress-induced relapse to heroin and cocaine seeking in rats: a review. Brain Research Reviews 33:13-33

Shaham Y, Shalev U, Lu L, de Wit H, Stewart J (2003) The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology 168:3-20

Epstein DE, Preston KL, Stewart J, Shaham Y (2006) Toward a model of drug relapse: An assessment of the validity of the reinstatement procedure. Psychopharmacology

Crombag H, Bossert JM, Koya E, Shaham Y (2008) Context-induced relapse to drug seeking: a review. Philosophical Transactions of the Royal Society B: Biological Sciences 363: 3233-3243

Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y (2011) Neurobiology of incubation of drug craving. Trends in Neuroscience 34:411-420

Sinha R, Shaham Y, Heilig M (2011) Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharmacology

Marchant MR, Li X, Shaham Y (2013) Recent developments in animal models of drug relapse. Current Opinion in Neurobiology

Bossert JM, Marchant NJ, Calu DJ, Shaham Y (2013) The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. Psychopharmacology 229:453-476

Calu DJ, Yu-Wei C, Kawa A, Shaham Y (2014) The use of the reinstatement model to study mechanisms of relapse to palatable food seeking during dieting. Neuropharmacology 76:395-406

Caprioli D, Venniro M, Shaham Y (2015) Animal models of drug relapse. Progress in Brain Research (invited review)

Courtesy of
Taco de Vries

Translational research

N-acetylcysteine

NK1 receptor antagonists

Alpha-2 adrenoceptor agonists

Alpha-1 adrenoceptor antagonists

Incubation of craving

Brain areas activated during cue-induced reinstatement (rats) and craving (humans)
(not discussed)

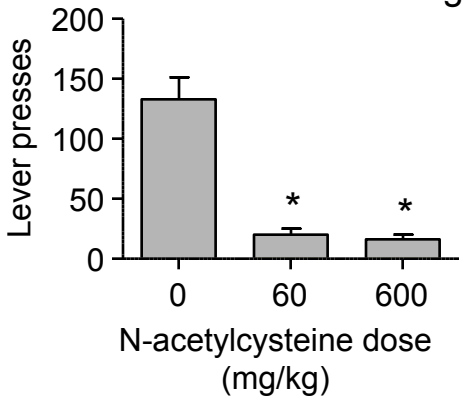
The reinstatement model and predictive (postdictive) validity

	Reinstatement results
Opiate maintenance therapy	Chronic minipump delivery of methadone, buprenorphine, and heroin decrease heroin-priming induced reinstatement
Naltrexone for alcohol	Naltrexone blocks alcohol-priming- and cue-induced reinstatement
Acamprosate for alcohol	Acamprosate blocks alcohol-cue-induced reinstatement
Varenicline for nicotine	Varenicline blocks nicotine-priming-induced reinstatement

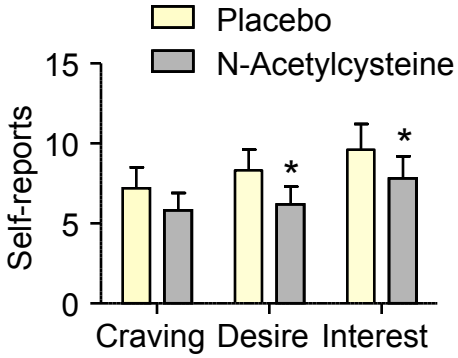
	Negative examples
Bupropion for nicotine	Acute bupropion potentiates cue-induced reinstatement
Amphetamine (cocaine addiction)	Acute amphetamine reinstates cocaine seeking

N-acetylcysteine

Rats: Cocaine-induced reinstatement of cocaine seeking



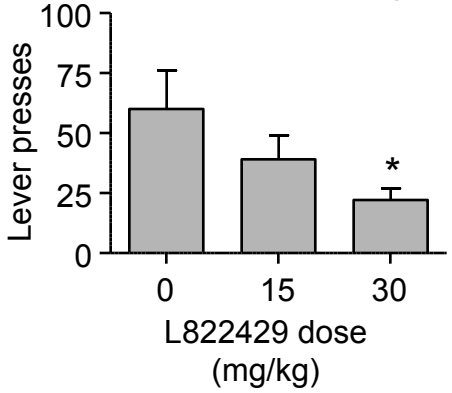
Humans: Cue-induced cocaine craving, desire, and interest



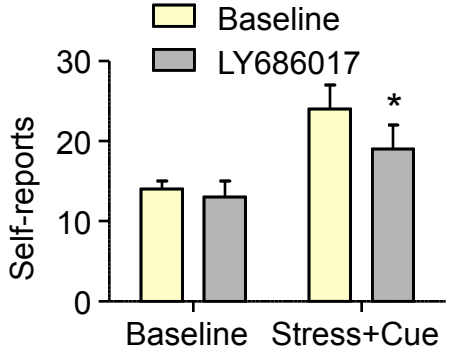
Baker et al. Nat Neurosci 2003
LaRowe et al. Am J Psychiatry 2007

NK1 receptor antagonist

Rats: Footshock-stress-induced reinstatement of alcohol seeking



Humans: Stress+cue-induced alcohol craving



Schank et al. Psychopharmacology 2011
George et al. Science 2008

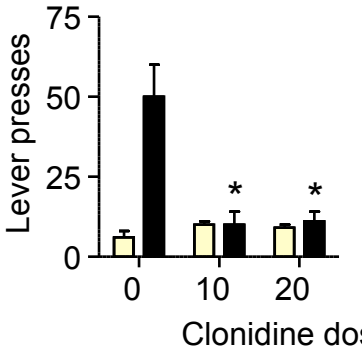
LaRowe et al. (2013) A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. Am. J. Addictions 22:443-452

CONCLUSION: While the present trial failed to demonstrate that NAC reduces cocaine use in cocaine-dependent individuals actively using, there was some evidence it prevented return to cocaine use in individuals who had already achieved abstinence from cocaine.

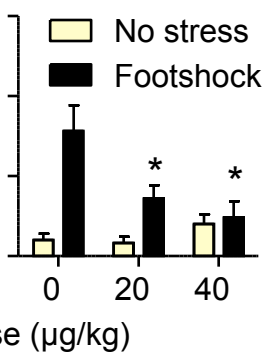
Alpha-2 adrenoceptor agonists

Rats

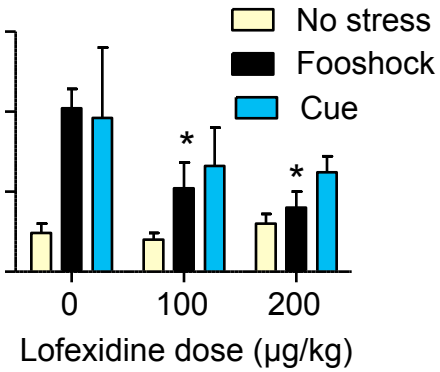
Heroin



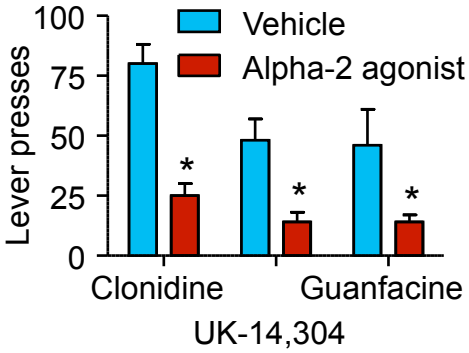
Cocaine



Speedball

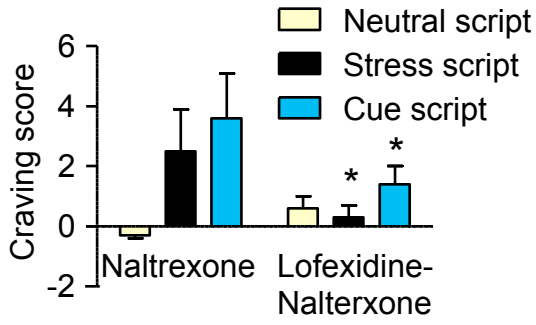


Cocaine
Cue reinstatement

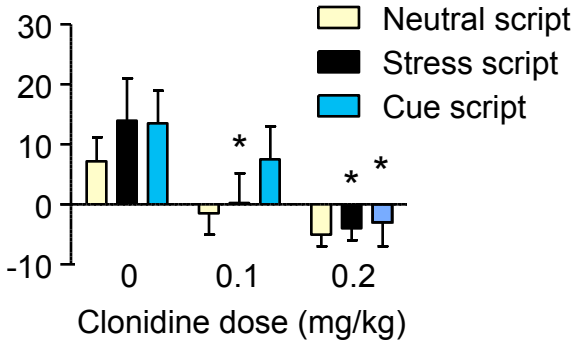


Humans

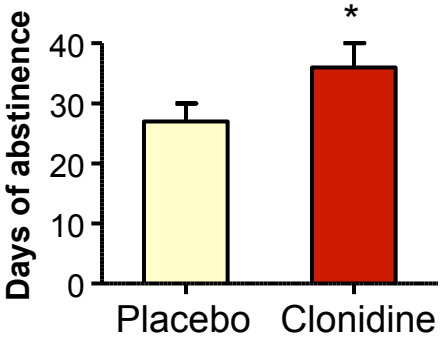
Heroin addicts



Cocaine addicts



Relapse prevention trial in heroin addicts on buprenorphine (# of abstinence days)

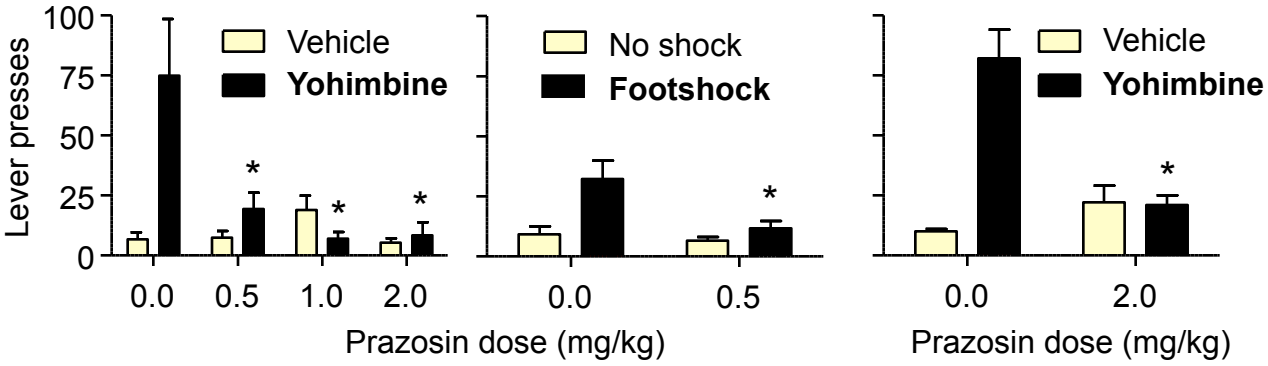


Rats: Shaham et al. EJN 2000; Erb et al. NPP 2000; Highfield et al. NPP 2001; Smith & Aston-Jones, Biol Psychiatry 2011
Humans: Sinha et al. Psychopharmacology 2007; Jobes et al. Psychopharmacology 2011; Kowalczyk, Preston et al. (submitted)

Alpha-1 adrenoceptor antagonists (prazosin)

Rats

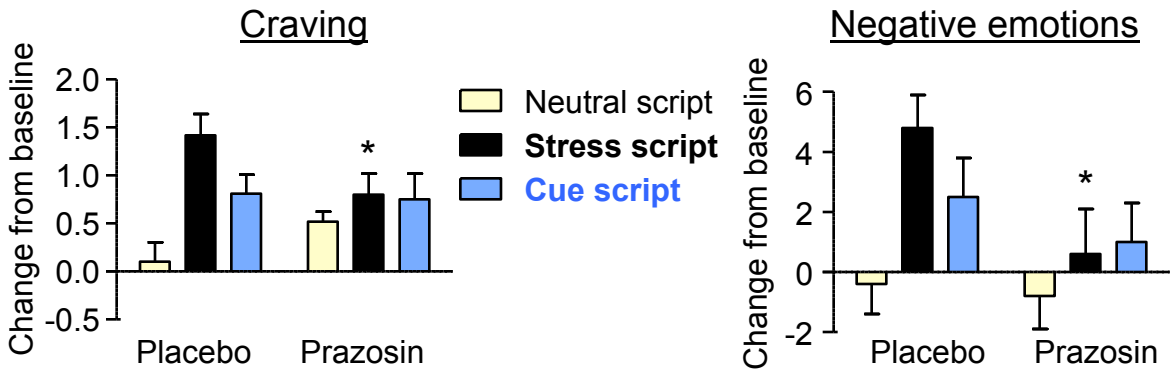
Alcohol



Palatable food

Humans

Alcohol addicts



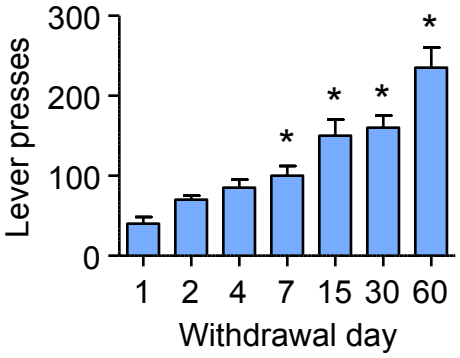
Le et al. Psychopharmacology 2011; Fox et al., Alcoholism: Clinical and Experimental Research 2011

Incubation of cue-induced drug craving

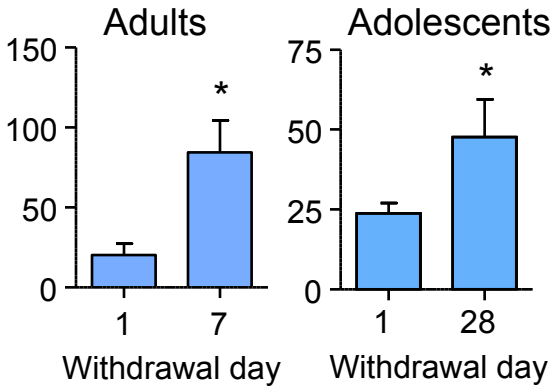
Rats

Behavioral data

Cocaine

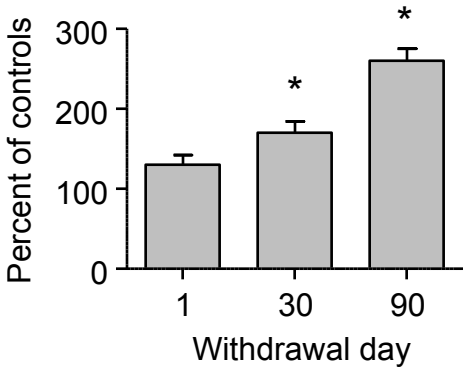


Nicotine



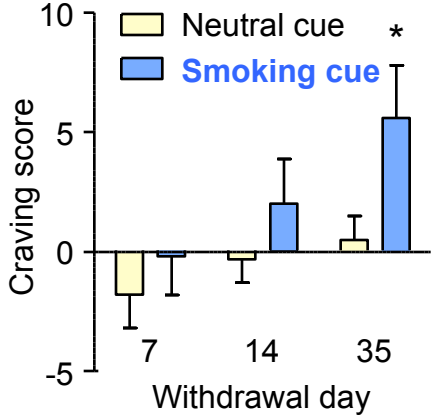
Neurobiological data (cocaine)

Nucleus accumbens BDNF

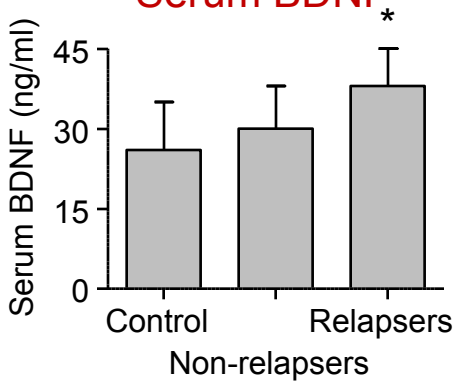


Humans

Nicotine



Serum BDNF



Rats: Grimm et al. Nature 2001; Grimm et al. JN 2003; Abdolah et al. EJN 2010; Le et al. unpublished
Humans: Bedi et al. Biol Psychiatry 2011; D'Sa et al. Biol Psychiatry 2011

Why are medication effects more robust and less variable in laboratory animals than in humans addicts?

Homogenous (laboratory animals) versus heterogeneous (human addicts) subjects

More flexibility and control over experimental parameters in laboratory animal studies than in human laboratory studies

Compliance with medication taking